CHIRON

**Statement Presented To**

**Committee on Government Reform**

**United States House of Representatives**

**By Howard Pien**

**President and CEO**

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**Introduction**

Mr. Chairman, Members of the Committee: Thank you for the opportunity to provide a statement to the Committee on Government Reform at today's hearing. I am Howard Pien, president and CEO of Chiron Corporation, a global biotechnology company headquartered in Emeryville, California with 2003 revenues of $1.75 billion. Founded in California in 1981, Chiron is composed of three business units: BioPharmaceuticals, Blood Testing and Vaccines. Chiron is dedicated to research and innovation addressing global public health challenges. Through Chiron's breakthrough research discoveries in the fields of hepatitis B virus, human immunodeficiency virus and hepatitis C virus, millions of potentially fatal infections have been prevented.

**Overview of Chiron Vaccines**

Chiron is the fifth-largest vaccines producer in the world, with sales of $678 million in 2003. Chiron Vaccines produces pediatric and adult vaccines to prevent life-threatening illnesses. These vaccines have protected millions of people globally from *N. Meningitidis* Group C, polio, measles and other potentially fatal diseases. Chiron is a leading supplier of oral polio vaccine, producing more than 800 million doses annually to support global polio eradication efforts. Our rich heritage in vaccines is traced to the three European manufacturers Chiron has acquired over the past two decades, all of which were founded 100 or more years ago. The company has production facilities in Liverpool, United Kingdom; Siena, Italy; Marburg, Germany; and Ankleshwar, India; and it carries out research in Siena, Marburg and Emeryville. Chiron has a successful record of product development, including the launch of the first recombinant vaccine against pertussis, the first adjuvanted influenza vaccine and a conjugate vaccine against *N. Meningitidis* Group C.

Chiron currently has two vaccines licensed in the United States: Fluvirin® influenza vaccine, one of only two injectable influenza vaccines approved by the U.S. Food and Drug Administration (FDA), and RabAvert® rabies vaccine. Fluvirin is indicated for immunization against the influenza vaccine strains contained in the vaccine for persons of four years of age and older. Chiron also supplies diphtheria and tetanus (DT) concentrate to GlaxoSmithKline for use in its DT-containing vaccines licensed by the FDA.[1]

**Influenza Immunization**

Vaccination of persons at risk from the complications of influenza is a key public health strategy in preventing morbidity and mortality due to the disease. Based on data from the 1990s, the U.S. Centers for Disease Control and Prevention (CDC) have estimated that influenza causes an average of approximately 36,000 deaths and 200,000 hospitalizations per year in the United States, with 90 percent of the mortality occurring in adults of ages 65 years and older.[2,3]. In order to minimize the burden of disease caused by the annual influenza epidemic, the following requirements, best achieved through public-private partnerships, must be met:

[1] Infanrix (DtaP) & Pediarix (DtaP-HepB-IPV)
[2] Source: Morbidity and Mortality Weekly Report 2003, Vol. 52 RR8
[3] Source: *JAMA.* 2004;292:1333-1340

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- An adequate, uninterrupted and sustainable supply of influenza vaccine to protect the population.
- Appropriate mechanisms to ensure delivery of the vaccine to the target populations.
- High public awareness on the need for immunization to ensure uptake of the vaccine by the target population.

**Chiron Support for Handling the Challenges of this Season**

Prior to October 5th, advance planning of activities for the 2004-2005 influenza season by the public and private sectors was based on the anticipation of a record supply of influenza vaccine, along with aggressive vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP) and increased public interest in influenza immunization following heightened awareness during the 2003-2004 season. The challenges the public sector expected for the upcoming influenza season involved fulfilling the new Vaccines for Children (VFC) entitlement for children ages 6-23 months old and people under 18 years of age who are close contacts of infants ages 0-23 months, as well as reducing ethnic and geographic disparities in coverage rates.

Over the past four weeks the public and private sectors under the leadership of the CDC have worked diligently to develop and implement a plan to meet the unanticipated supply shortage. One of the key issues that needed to be addressed was allocation of the remaining doses of influenza vaccine; accordingly, a plan was developed to distribute scarce influenza vaccine to providers most likely to be able to reach high-risk patients. Clearly, a key piece of information in developing the plan was learning the destinations and volumes that had been projected for Fluvirin. While Chiron was not able to provide information down to the level of end-user as it does not supply vaccine directly to physicians and clinics, it was able to assist the CDC by facilitating contact with the seven distributors who handle Fluvirin, as well as providing additional information requested by the CDC. Chiron has chosen a distributor based model as this ensures that its influenza vaccine can be rapidly and efficiently distributed to thousands of sites all across the country.

The primary focus of Chiron's activities over the past few weeks has been to work closely with the regulatory authorities to develop a remediation plan to address the issues the two regulatory agencies have raised about its Liverpool facility. Chiron's primary concern at this time is to be in a position to supply influenza vaccine to the United States for the 2005 - 2006 influenza season in order to ensure that there is an adequate supply of vaccine available.

**Chiron Remediation Activities**

Chiron is developing a robust remediation plan that, pending approval by the Chiron Board of Directors, will set Chiron on the path towards achieving our goals in the right time frame. We have discussed our with both the FDA and the UK Medicines Healthcare

products Regulatory Agency (MHRA), and Chiron plans to continue working with both agencies to achieve our common goal of ensuring the Liverpool facility is in a position to supply influenza vaccine next season.

The comprehensive remediation plan developed addresses quality systems in a holistic manner, going beyond merely responding to specific regulatory observations. Our remediation activities are concentrated in three primary areas:

- Manufacturing: Manufacturing processes, practices and techniques.
- Quality systems: The quality systems used in the manufacturing, testing, and lot evaluation process.
- Governance: Management of people and handling of issues.

Within each manufacturing area Chiron intends to address issues surrounding: what it does, how it does it, who does it and why, what resources are needed, and how the quality of the output is checked.

Leadership is a critical success factor in executing a task as complex as the remediation plan in the short time frame required. Effective November 3, I reorganized Chiron's senior management team to allow me to focus more attention on overseeing the remediation activities and quality improvement. We have created the position of Chief Operating Officer on an interim basis, and Chiron's COO will oversee other parts of our diverse organization to ensure that Liverpool remediation is my top corporate priority for Vaccines.

Our internal experts, transferred from Chiron Corporation business units across the globe, and external consultants will focus on addressing the underlying, fundamental issues that have been uncovered and on developing a robust quality system at our Liverpool facility. Chiron understands the urgency of the situation and is acting with expediency and diligence to redress our Good Manufacturing Practices (GMP) deviations and to execute effectively a robust remediation plan.

**Influenza Vaccine Supply Overview**

Ensuring an adequate supply of influenza vaccine for the United States is a key component of any strategy for reducing the burden of influenza disease. A critical success factor for securing an uninterrupted influenza vaccine supply over the long term is the creation of a sustainable market for influenza vaccine: one where favorable conditions exist to enable manufacturers to invest and expand. The market conditions required to create a positive environment include but are not limited to:

- Sufficient demand for the vaccine to ensure that production capacity for the vaccine is utilized.
- Levels of pricing for the vaccine that justify investments by producers in maintaining existing production capacity and, if required, encourage investment in additional capacity.

- A regulatory regime that fosters innovation in the enhancement of existing technologies and development of new technologies while ensuring the safety of available vaccines.
- A mechanism for protecting influenza vaccine producers from liability issues.

In the 1990s, the environment was not conducive to encouraging investment in influenza vaccine manufacturing capacity due to a combination of factors, primarily low pricing and stagnant demand. This environment was an important contribution to the exit of several manufacturers of influenza vaccine resulting in supply constraints on the US market. Over the last few years, however, the trend has been reversing. The market has expanded due to broadened recommendations on influenza immunization by the ACIP to include individuals between 50 and 64 years of age, healthy children between 6 and 23 months of age, and close contacts of children aged up to 23 months of age[4]. Pricing of influenza vaccines has reached a level that allows manufacturers to invest in maintaining facilities to meet rising FDA standards and in expanding manufacturing capacity in order to meet the increased demand. Finally, reimbursement rates for providing influenza vaccine injections have increased to levels at which physicians are encouraged to actively immunize patients, raising coverage rates.

The changes in the business environment, especially the price increases that have occurred over the past three years, have reversed the trend of decreasing manufacturing capacity. Producers are investing in capacity increases, upgrading facilities and licensing cutting-edge technologies for the United States. However, given the nature of biologics manufacturing, there is inevitably a lag between the decision to invest and improved capacity as a result of that investment. The United States is only now beginning to see the impact of the positive changes in market dynamics that occurred a few years ago. For example, Chiron has committed $100 million dollars to replace its existing influenza bulk manufacturing facility with a new "state of the art" facility[5] to complement the secondary manufacturing facility opened in 1998. This commitment is being made to support Chiron's ability to supply Fluvirin to the United States and to add incremental capacity, if required, until new technologies such as cell-culture production are sufficient to meet the needs of the United States.

**Diversification of Influenza Vaccine Supply**

The supply shortage that the United States currently faces this season has served to highlight an additional dimension required for this country to achieve ***"influenza vaccine security,"*** diversification of sources of supply. ***"Influenza vaccine security"*** is defined as access to an uninterrupted and sustainable supply of safe and effective influenza vaccine to satisfy annual demand under routine epidemic circumstances.

Prior to this season, the focus of public health had been on volume of production: ensuring that production capacity was at a level sufficient to make certain that an adequate supply of influenza vaccine was available to meet demand in inter-pandemic

[4] Source: Morbidity and Mortality Weekly Report 2004 Vol 54: RR6.
[5] A new fill/finish facility was completed a few years ago.

years. Arguably, the influenza vaccine supply situation was much less fragile than for many other commonly used vaccines in the United States. The Institute of Medicine Report "Financing of Vaccines in the 21st Century; Assuring Access and Availability"[6] highlighted the fact that for six of the recommended vaccines[7] in the United States, there is a single source of supply. Should a manufacturer of one of these vaccines experience production problems or other disruptions, there is no backup capacity available. This situation creates significant potential for supply interruptions, and, indeed, these have occurred over the past few years. In 2001 and 2002, eight of the 11 recommended childhood vaccines were in short supply.[8] These shortages had an impact on immunization policy in the United States, forcing the ACIP to temporarily revise its recommendations on pneumococcal conjugate vaccine and diphtheria, tetanus and pertussis (DtaP) and to recommend that varicella (chicken pox) immunization be pushed back to 18-24 months from 12-18 months. In contrast, there are three sources of supply for influenza vaccine, making a complete disruption of supply an unlikely event. Regrettably, the events of this season have highlighted a flaw in this argument, related to the nature of influenza vaccine production and use.

This season's experience has shown the risk of dependence on two production facilities to supply the majority of influenza vaccine for the United States. A significant problem at either of the two facilities could reduce supply by as much as 50 percent, creating significant challenges for the public health infrastructure. Essentially, while a complete disruption of supply is unlikely, the potential for a major shortfall exists if only two facilities provide approximately 95 percent of the vaccine used in the United States.

Due to the seasonal nature of influenza immunization, the inability to stockpile vaccine and the cycle-times for influenza vaccine production, the public health system has little time to react to such a shortfall. It is not possible to secure alternative sources of supply of influenza vaccine in the volumes that would be required, as little excess capacity is available on the global market. Therefore, based on the lessons learned from this season, diversification of influenza supply, reducing the dependence of the United States on the two production facilities that currently supply 95 percent of demand, is an important component if the United States is to achieve influenza vaccine security.

Accomplishing the diversification of the manufacturing base of influenza vaccine supply is not a simple task and poses significant short and long-term challenges. In the short-term, this requires identification of existing suppliers who not only have spare capacity but also are capable of meeting FDA standards in terms of clinical data and compliance with U.S. standards of GMP. Once such suppliers are identified they must go through a review of their data by the FDA. Expediting this process while ensuring that vaccines meet U.S. regulatory standards represents a significant challenge. Simply building a new

[6] Institute of Medicine, August 2003
[7] Tetanus-diphtheria, measles-mumps-rubella, varicella (chicken pox), pneumococcal conjugate, meningococcal polysaccharide, pneumococcal polysaccharide
[8] USA Today, February 18, 2002

production facility for the United States is not a short-term option, as it would take five or more years to develop and license a new influenza vaccine production facility[9].

In the long term, the challenge for diversification of the manufacturing base is even more complex, as any solution must be sustainable if it is to ensure an uninterrupted supply of influenza vaccine. Attracting new entrants into the influenza market is only the first step to reducing the chances of disruption. Conditions must be created such that both the new entrants and the existing suppliers remain in the market over the long haul. The challenge therefore goes beyond finding new entrants; the challenge is to create a market environment that is conducive to supporting multiple manufacturers of influenza vaccine. Recent experience serves to illustrate the inherent difficulty of accomplishing this objective. In the late 1990s the United States had four licensed suppliers of influenza vaccine, three of which were located in the United States. Due to market conditions two of the four ceased production. Similar lessons can be gleaned from the experience with another vaccine, tetanus-diphtheria (Td) where prices in the range of $1.00 per dose led to the exit of several manufacturers leaving a single source of supply[10]. Many of the lessons learned from these experiences are applicable to the future of influenza vaccines. It is essential that vaccine prices are at a level sufficient for producers to invest in maintaining and upgrading manufacturing facilities, and that sufficient demand for influenza vaccine is created to ensure utilization of existing production capacity and development of additional capacity. If these conditions are not met over the long-term history will repeat itself, and the number of manufacturers of influenza vaccine will inevitably shrink as the market will not be attractive enough to justify continued investment.

In the last few years, the United States has come a long way towards creating incentives that encourage manufacturers to invest in capacity and physicians to acquire and administer the influenza vaccine. Appropriate reimbursement rates for influenza vaccine purchase and administration are important, particularly through Medicare as the vaccine is universally recommended for those sixty-five years of age and older. Therefore, the decision by the United States Congress to continue reimbursing the vaccine at 95 percent of the Average Wholesale Price (AWP) and to continue the current practice of updating this reimbursement rate on a quarterly basis as established in the Medicare Modernization Act was extremely important in creating a positive environment. The price that the Federal Government has negotiated for purchase of the vaccine through its Vaccines for Children program, which will be expanding its purchase of influenza vaccine due to the new recommendations, also sends a strong signal to manufacturers that there is recognition that pricing of influenza vaccine must be at a level that permits continued investment by producers.

Administration fees are an important mechanism for encouraging demand for influenza vaccine, as they can create an incentive for physicians to actively immunize their patients. The trends in this area over the last few years, such as the increased focus that

[9] Source: Chiron internal estimate.

[10] Sanofi-Aventis is the sole source of supply although small quantities of tetanus vaccine are available from the Massachusetts Public Health Biologic Lab.

Centers for Medicare and Medicaid Services (CMS) has placed on prevention and preventive health services, are extremely encouraging. In 2003, CMS increased administration rates by roughly 90 percent to between $6.00 and $8.00 from less than $4.00, motivating physicians to actively immunize their patients. On November 3, CMS announced that in 2005 it will further increase payment rates to physicians for administration to $18.00[11]. In addition, physicians will now be paid for performing the injections even when they are performed as part of other Medicare-covered services, which was not permitted previously.

**Demand for Influenza Vaccine**

Recommendations, *"who should get the vaccine",* and coverage rates, "*who actually gets the vaccine"*, are two significant factors that generate demand for influenza vaccine. Therefore, having the right recommendations in place and making the programs, infrastructure and incentives available to achieve high coverage rates are crucial factors in creating an attractive environment for manufacturers of influenza vaccine. These factors are key to driving demand and demand will drive supply.

Currently, United States recommendations are fairly broad compared to most countries[12]. At present roughly 60 percent of the U.S. population is covered by the recommendations, and it is estimated that 185 million individuals fall into the recommended categories. Over the last few years, the ACIP recommendations on influenza vaccine have been expanded with the addition of additional cohorts. In 2000, the ACIP recommended immunization for individuals between 50 and 64 years of age because of the prevalence of high-risk conditions in this group. Influenza vaccine was recommended for this entire age group to increase the low vaccination rates among persons in this age group with high-risk conditions[13]. In 2004, influenza immunization was recommended for infants between 6 and 23 months of age, primarily due to the increased risk of morbidity and mortality in this age group, and close contacts of infants up to 23 months of age. In the future, the recommendations may be broadened even further. The ACIP has added language to its Recommendations on Prevention & Control of Influenza stating "*ACIP plans to review new vaccination strategies for improving prevention and control of influenza including the possibility of expanding recommendations for use of influenza vaccines"*[14].

Recommendations represent the first step in creating demand. Achieving high coverage rates is the critical second step to generating demand for influenza vaccine and, while progress has been made, the United States still has a long way to go in implementing its recommendations. As mentioned in the previous paragraph, 185 million Americans are

[11] Source: CMS Office of External Affairs Press Release November 3, 2004

[12] Most major European countries, for example, recommend vaccination in individuals 65 and older and high risk groups only.

[13] Age-based strategies are more successful in increasing vaccine coverage than patient-selection strategies based on medical conditions. In addition, individuals aged between 50 and 64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and reduced need for medical visits and medication.

[14] Source: Morbidity and Mortality Weekly Report Volume 53

covered by the recommendations, yet in 2003-2004 only 83 million Americans were vaccinated, which represented the highest immunization rate ever for influenza immunization[15]. Progress has been made in raising immunization coverage rates, particularly in individuals aged 65 and older. However, significant improvements are needed, particularly for individuals between 50 and 64 years of age, infants aged 6-23 months, and children and healthy adults in close contact with people at high risk.

Over the last decade, the United States has had success in raising immunization coverage rates for individuals above 65 years of age. Data analyzed from the Behavioral Risk Factor Surveillance System (BRFSS) in 1993 indicated that 50 percent of respondents reported having received influenza vaccine compared to 66 percent in 2002[16]. This represents significant progress but is still below the 90 percent goal set for non-institutionalized adults in the Healthy People 2010 Objectives[17] and has remained level since 1997.[18] Continued investment in patient education and ensuring access to vaccine will be required if coverage rates are to continue to increase for individuals 65 years of age and older. Achieving higher coverage rates will increase in importance over the next few years as influenza is expected to have an increasingly serious impact in the United States due to the aging population. Therefore, having effective strategies in place to prevent the disease through immunization will become increasingly important if the burden of disease is not to increase.

Individuals between 50-64 years of age are another population that benefit significantly from influenza immunization as this population has an increased prevalence of high-risk conditions.[19] Despite the universal recommendation being in place for several seasons only 36 percent of respondents between 50 and 64 years of age in the 2002 BRFSS reported having received influenza vaccine during the previous 12 months, well below the level of respondents above 65 years of age. Significant efforts need to be invested in reaching this age group for the following reasons. First, roughly one third of the individuals in this age group are estimated to suffer from conditions such as chronic disorders of the pulmonary or cardiovascular systems, including asthma and metabolic diseases such as diabetes that put them at higher risk of complications due to influenza. Second, in the longer term, achieving high influenza coverage rates in this age group will translate to future higher coverage rates in the 65 and older population. It is likely that an individual who is in the habit of getting an annual influenza vaccine is likely to continue to do so as he or she ages.

As mentioned previously the ACIP included influenza immunization in the routine pediatric immunization calendar for the first time this season. Therefore, it is too soon to assess coverage rates in this cohort. However, a baseline is provided by data collected by the CDC in the 2002 and 2003, when the recommendations encouraged that, when

[15] Source: CDC
[16] Source: Morbidity and Mortality Weekly Report 1996, Vol 45 No 40; Morbidity and Mortality Report 2003, Vol 52 No 41
[17] Objective no 14.29 at www.health.gov/healthypeople/
[18] Source: Morbidity and Mortality Weekly Report 2003, Vol 52 No 41
[19] Approximately 30 percent of the 42 million persons in the United States between 50 and 64 years of age have one or more high-risk medical conditions.

feasible, children 6 to 23 months of age receive influenza vaccine each season.[20] Roughly four percent of children received two doses of influenza vaccine while approximately seven percent received at least a single dose. This suggests that significant efforts will be required to raise coverage rates in the pediatric population to levels that are similar for other routinely recommended pediatric vaccines which, in 2003, ranged from approximately 70-90 percent[21]. However, given the successes that the United States has had in adding new antigens to the pediatric immunization schedule over the last few years, it seems safe to assume that this goal will eventually be reached, reducing the burden of influenza disease in children.

Immunization of contacts of high-risk individuals represents an important strategy for protection of persons at high-risk for complications from influenza. Persons who are clinically or sub-clinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might therefore cause a reduction in influenza-related deaths and hospitalization among high-risk populations. Health-care workers (HCWs), due to the nature of their occupation, are often in contact with high-risk individuals and therefore the ACIP and other major medical groups and nursing organizations have recommended that HCWs should be vaccinated against influenza. Despite the recommendations, coverage rates among HCWs are less than 40 percent.[22] Chiron believes that significant efforts need to be devoted to increasing immunization coverage rates in this group. First, improving coverage rates will protect health-care workers, their patients and communities. This will improve prevention, patient safety and reduce the disease burden. Second, health care workers are an important source of information on immunization to the general population and must lead by example. An unvaccinated healthcare worker is not a credible advocate for immunization. Therefore, a first step to convincing the general public to get immunized against influenza is ensuring that health care workers are vaccinated.

In order to raise coverage rates among health care workers Chiron believes the following is needed:

- HCWs should be provided with easy access to influenza vaccine.
- Resources should be committed to institutionalizing immunization of HCWs in their workplace.
- Professional health care organizations should develop policies to support immunization of HCWs and encourage constituents to educate HCWs about the benefits of immunization.
- HCWs influenza immunization rates should be regularly measured and reported.

In this context, Chiron supports the recommendations made by the National Foundation of Infectious Disease in its call to action, *Influenza Immunization Among*

[20] Source: Morbidity and Mortality Weekly Report 2004, Vol 53 No 37
[21] Source: National Immunization Program 2003 National Immunization Survey
[22] Source: Morbidity and Mortality Weekly Report 2003, Vol. 52 RR8

*Healthcareworkers*[23], and encourages professional health care organizations and institutions to follow them.

Prior to this influenza season, Chiron felt that substantial and innovative efforts were required to raise influenza immunization coverage rates in the groups for whom influenza immunization was recommended.[24] The events of this season only serve to magnify the need for such efforts. Even greater efforts will be required once the current challenges have been addressed and we return to a normal supply situation. One of the consequences of the shortage of influenza vaccine this season has been a significant shift in the emphasis of communication activities. This season, communication efforts on influenza have shifted away from a focus on encouraging influenza immunization to communicating the steps necessary to deal with the shortage. Since October 5, messaging has been focused on communicating the priority groups that should receive vaccine, asking others to step aside and highlighting respiratory hygiene and other preventative measures. Essentially, as a result of the shortage, many of the individuals who would normally be encouraged to *roll up their sleeves* and seek immunization are being asked to *roll down their sleeves* this year. If the supply situation returns to normal next season significant efforts will be needed to ensure those who properly stepped aside this season return and get immunized. In addition, renewed efforts will be needed to encourage those who never got vaccinated to seek immunization.

As the U.S. influenza supply is stabilized and diversified, there are key public health issues that need to be addressed:

- Raising awareness of the immunization recommendations among the medical community and general population.
- Dispelling some of the myths about influenza vaccine that exist, e.g. *"I can get influenza from the vaccine."*
- Encouraging immunization by highlighting the benefits of immunization and developing innovative programs for facilitating access to the vaccine.
- Extending the immunization season into December to increase the window in which vaccine could be supplied to the market.

The success that public-private partnerships have had in facing the challenges of this influenza season has served to reinforce Chiron's belief that collaboration between the public and private sector is the best means of increasing coverage rates. Comprehensive efforts need to be continued persistently and consistently over the next few seasons. Going forward sharpening the focus on the objective of the Healthy People 2010 goals of 90 percent coverage rates of non-institutionalized adults 65 years of age and older and 60 percent coverage rates of high-risk non-institutionalized adults 18-64 years of age is of critical importance[25]. The National Influenza Vaccine Summit, organized by the

[23] http://www.nfid.org/publications/hcwmonograph.pdf
[24] Statements to Government Reform Committee February 12, 2004 and to Senate Committee on Aging September 28, 2004.
[25] The target rate for institutionalized adults aged 18 and older is 90 percent.

American Medical Association in collaboration with the CDC, which brings together key stakeholders in the public and private sectors is a vehicle that has worked to help face the challenges of this season and is well placed to lead the efforts to raise coverage rates once influenza vaccine supply returns to normal levels.

**Pandemic Preparedness**

An influenza pandemic occurs when there is a major change (shift) in the influenza virus such that the majority of the world's population has not been previously exposed to the strain and is therefore extremely vulnerable to the virus. Influenza pandemic is a major public health threat with the potential to cause a rapid increase in morbidity and mortality. Three pandemics have occurred in the 20th century, the first in 1918. It is estimated that approximately 500,000 deaths due to influenza occurred in the United States between September 1918 and April 1919 and that the pandemic caused 20 million deaths worldwide. The 1918–1919 pandemic was the worst pandemic recorded, and mortality in more recent pandemics has been lower. The Asian influenza pandemic of 1957 is estimated to have caused approximately seventy thousands deaths in the United States, while the Hong Kong influenza pandemic of 1968 is estimated to have caused 33,000 deaths.

The use of antiviral drugs, public health measures such as quarantine and immunization of individuals with a pandemic strain-specific vaccine are likely to be important public health interventions for preventing the spread of disease and limiting the morbidity and mortality from pandemic influenza. The lessons learned this season in implementation of a prioritization scheme and in allocation and distribution of a limited amount of vaccine will be extremely useful in developing plans for vaccine distribution and allocation in the event of a pandemic.

The supply challenges experienced this season provide a preview of some of the challenges that will be faced in the event of a pandemic. The cycle time for production of influenza vaccine means that there will be a six-month lag between the isolation of the pandemic strain (followed by a decision to produce a vaccine against the strain) and the actual availability of the vaccine. In addition, quantities of vaccine will initially be limited. Therefore, there will be similarities to the current influenza season as the public health community will be faced with the allocation of a scarce commodity in order to ensure that it provides maximum benefit to the United States. Thus, it seems important that the following issues are resolved prior to the onset of a pandemic:

- Development of a prioritization scheme identifying who should receive priority in getting the vaccine.
- Determination of responsibility for decisions on vaccine allocation
- Identification for mechanisms for distribution of vaccine. For example, will it be the current system, a completely new primarily public sector system or a hybrid?

Resolution of these challenges in advance of a pandemic should occur as otherwise pandemic response might be hindered. There are parallels between the experience of this season and the pandemic situation. Therefore the lessons learned in handling the challenges currently faced may assist in the formulation of pandemic strategy.

A plan for allocation and distribution of vaccine in the event of a pandemic is of no value without the availability of a vaccine to distribute. It is therefore crucial for steps to be taken to ensure a pandemic vaccine can be developed as quickly as possible in the event of an influenza pandemic. Therefore, the world is fortunate that the National Institute of Allergy and Infectious Diseases (NIAID) has had the foresight as part of the NIAID Influenza Pandemic Preparedness Plan to support the manufacture and production of a candidate vaccine against potential pandemic strains of avian influenza. Chiron is participating in these efforts and believes partnerships between industry and governments are crucial to ensure the availability to the public of safe and effective vaccines against avian influenza as soon as possible. The need for additional investments should be evaluated once the results of these trials are available.

It is important to note that the current regulatory approval process would have to be expedited in order for manufacturers to rapidly convert to producing a monovalent pandemic vaccine in a timely fashion. Under the present system, obtaining regulatory approval could be a bottleneck in supplying pandemic vaccine. Discussions and planning should occur now between manufacturers and the FDA in order to determine the regulatory pathway for approval of a vaccine, including any amendments to official release requirements in the event of a pandemic. This would be of significant value to expedite the availability of supply should the pandemic occur.

From the perspective of an influenza vaccine producer, planning for a pandemic represents a significant challenge due to the nature of influenza vaccine production. Essentially, the following factors limit the ability to rapidly expand supply in the face of a pandemic under current circumstances:

- **Production capacity**—Influenza vaccine production capacity is aligned with annual demand for vaccine under normal circumstances, i.e., between pandemics, and therefore little or no surge capacity exists to meet pandemic demand.
- **Inability to stockpile**—Stockpiling of vaccine in preparation for a pandemic is not a viable strategy, as it is not possible to predict the strain that will cause the pandemic.
- **Supply of primary production material**—Currently, vaccines are produced using eggs, and ensuring an adequate supply of eggs to significantly increase production during a pandemic represents a significant challenge.
- **Specialized production facilities**—Additional quantities of vaccine could not be readily produced in facilities used for other vaccines, as production and purification equipment and facilities are specifically designed for influenza vaccines.

Looking forward, in the event of a pandemic, Chiron will strive to fulfill its responsibility to supply vaccine to the United States and international markets. To increase vaccine production, Chiron would undertake year-round production of a monovalent vaccine. Influenza vaccine production would be run continuously over the whole year as opposed to the current seasonal production cycle. However, it should be noted that this assumes that additional egg supply will be available to keep the facilities running year round. A monovalent vaccine containing the pandemic strain only would be produced as opposed to the standard trivalent vaccine containing three strains. Manufacturing capacity would therefore be increased by a factor of three, assuming that the vaccine contains the same amount of antigen as the conventional influenza vaccine.[26] Any increase in the antigen content of the pandemic vaccine would result in a proportional reduction in the number of doses that could be produced. As mentioned previously, the clinical data available to support the definition of the pandemic vaccine will be increased significantly by the trials planned by the NIAID.

Chiron estimates that implementing these two steps in the event of a pandemic would more than triple its influenza vaccine manufacturing capacity, assuming the pandemic vaccine contains the same amount of antigen as the normal vaccine. By the end of the decade, under its current plan, Chiron anticipates being able to increase its pandemic vaccine production by an additional 50 percent due to expanded production capacity in Liverpool and the availability of a cell-culture facility in Marburg.

In the face of a potential influenza pandemic, switching production to a monovalent pandemic vaccine imposes a significant financial risk. If the predicted pandemic failed to materialize, there would be no demand for the monovalent vaccine, and Chiron would be forced to destroy the vaccine. Therefore Chiron would be unlikely to make the decision to switch production from trivalent vaccine to a monovalent pandemic strain without a guarantee of mitigation of the downside risks it would face in the event of the pandemic not materializing. Further, Chiron would be unable to assume this risk without financial guarantees being in place due to the severe consequences of losing an entire year's revenues generated from the production of influenza vaccine. Therefore, in order to trigger a switch to pandemic vaccine production as quickly as possible in the event of a potential pandemic, governmental contract authority to purchase pandemic vaccine production by an agreed-upon mechanism of compensation should be in place prior to a pandemic. Such a contractual agreement between vaccine manufacturers and the government implies a limited role for the private sector in the marketing of a vaccine in the event of a pandemic. National governments would procure the vaccine, be responsible for its distribution and determine the priority of immunization. The events of this season have served to reinforce Chiron's belief that, in the event of a pandemic, the Department of Health & Human Services (HHS) will play a significant and crucial role in prioritization, allocation and distribution of the vaccines, even if the latter occurs through private sector channels.

[26] It should be noted that studies of experimental vaccines produced in response to the avian influenza A outbreaks in Hong Kong suggest that a greater dosage or an adjuvanted vaccine may be required. Therefore, whether this assumption will turn out to be valid is open to question.

Chiron recommends that a mechanism for indemnifying manufacturers, similar to that for smallpox and swine flu, be established in advance of a pandemic situation. The U. S. Government must address the considerable liability issues that manufacturers will face in a pandemic manufacturing situation. Under section 304 of the Homeland Security Act of 2002, "covered persons," including manufacturers, are deemed to be Public Health Service employees, so that the United States is the exclusively liable party under the FTCA for any injury or death arising out of the administration of a "covered countermeasure" against smallpox during an "effective period" defined by HHS declaration.[27] It is vital that Congress enact a similar provision for manufacturers producing influenza pandemic vaccines. Chiron welcomes the fact that section 890 of the American Jobs Creation Act of 2004, signed by President Bush on October 22, 2004, added trivalent influenza vaccine to the list of taxable vaccines included in the National Vaccine Injury Compensation Program.[28] However, in the context of this issue, it is important to note that coverage of a pandemic vaccine under this mechanism would be inappropriate due to concerns about the financial security of the fund as well as the very nature of a pandemic situation with regard to the volume of vaccine that would be administered in a pandemic situation.

Despite a potential increase in the supply of vaccine by a factor of greater than three, there still will be a global shortage of influenza vaccine in the event of a pandemic. Demand for influenza vaccine would increase dramatically compared to normal circumstances due to the need to immunize most of the global population and a potential increase in the number of doses required per person to provide immune protection from one to two. Current global influenza vaccine production capacity, estimated at roughly 300 million doses in a typical year,[29] will most likely be unable to cope with global demand, and therefore a shortage of vaccine is expected to occur.

Chiron is committed to maintaining supply to the United States in the event of a pandemic. However, the current location of Chiron's influenza manufacturing facilities outside of the United States imposes constraints on its ability to ensure this occurs, as it is not clear how global allocation of the vaccine will take place in the event of a pandemic. Where demand outstrips supply, it is possible that national authorities will impose constraints on the allocation of influenza vaccine by manufacturers under their jurisdiction. One of the constraints that may be imposed by national authorities is that producers be required to give priority to meeting national demand before shipping vaccine supply to traditional markets. For example, Chiron could be asked to give precedence to the United Kingdom in allocating vaccine supply from its Liverpool facility, as it is the only domestic source of supply for that country. Furthermore, once the needs of the United Kingdom were met, priority might be given to other European countries before allowing vaccine to be made available to the rest of the world. In addition, manufacturers with facilities located in European Union countries may be required by their national authorities to give precedence to the needs of other EU member countries-once domestic needs have been met-before vaccine can be exported outside of

[27] *See* 42 U.S.C. § 233(p)(1)-(2), (7).
[28] *See* H.R.4520 sec 890.
[29] Chiron internal estimate.

the EU, particularly for those member states that do no not have domestic production capacity. These variables are real and uncharted. Chiron believes it is important for the United States, United Kingdom and EU authorities to engage in discussions on pandemic influenza vaccine supply in advance of an outbreak in order to clarify supply priorities for its Liverpool facility. Chiron would welcome the opportunity to participate in these discussions.

An influenza pandemic will represent a significant challenge to Chiron, as it will need to rapidly expand influenza vaccine production at the expense of other products in its portfolio. Recognizing this challenge, Chiron is committed to supporting global pandemic preparedness efforts prior to (and during) the inevitable occurrence of a pandemic. Chiron believes that the lessons learned from handling this season's shortage can be extremely useful particularly with respect to policies for prioritization, allocation and distribution of pandemic vaccine. In addition, Chiron believes that the strategic public education programs that it considers crucial to increase demand for influenza vaccine during interpandemic years to assure a sustainable and uninterrupted supply of influenza vaccines will benefit U.S. pandemic preparedness. A strong, preferably domestic, influenza vaccine manufacturing base will ensure that the United States has an adequate supply of vaccine in the event of a pandemic. In addition, raising coverage rates will enhance the ability of the public health system to cope with the challenge of administering large amounts of vaccine to the population over a relatively short time frame. The annual influenza campaign provides a means of testing the preparedness and improving the capacity of our infrastructure to deliver and administer vaccine in the event of a pandemic or other bioterror threat.

**Conclusions**

The challenges of this season and the way they are being addressed have reinforced Chiron's belief that going forward significant efforts are required to raise immunization coverage rates and that public partnerships are the best way to accomplish this goal. Raising demand is a key element to creating a sustainable market for influenza vaccine, critical for ensuring an uninterrupted supply of influenza vaccine from a diversified manufacturing base over the long-term. This is an essential component in helping position the United States for preparedness for a global influenza pandemic by helping assure a supply of vaccine. If the lessons learned from coping with shortages of vaccine this season are applied the challenges of this season may offer a significant long term benefit by strengthening the ability of the United States to deal with the annual influenza epidemic and a potential pandemic.

Thank you for the opportunity to present the views of Chiron Corporation. I am happy to answer any questions you may have for me.